Synthesis of Isoxazolo[5,4-*b*]pyridines by Microwave-Assisted Multi-Component Reactions in Water

Shu-Jiang Tu,* Xiao-Hong Zhang, Zheng-Guo Han, Xu-Dong Cao, Shan-Shan Wu, Shu Yan, Wen-Juan Hao, Ge Zhang, and Ning Ma

School of Chemistry and Chemical Engineering, Xuzhou Normal University, Key Laboratory of Biotechnology for Medicinal Plant, Xuzhou, Jiangsu 221116, P. R. China

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A series of new polycyclic-fused isoxazolo[5,4-*b*]pyridines were obtained by a one-pot tandem reaction under microwave irradiation in water. Without any use of additional reagent or catalyst, the synthetic protocol represents a green one and makes this methodology suitable for library synthesis in drug discovery efforts.

Introduction

One of the main challenges in medicinal chemistry is the design and synthesis of biologically active molecules. The discovery of high-throughput screening (HTS) has tremendously increased the need for new testing compounds. In recent decades, combinatorial chemistry,[1−5] a technique that allows for the synthesis of large numbers of molecules, has changed the nature of chemical discovery.

Small-molecule combinatorial libraries are powerful tools for the interfacing of chemistry with biology because small molecules often have the ability to selectively manipulate the activity of biological systems.[6] Isoxazole is one of important heterocyclic units, which has been widely used as a key building block for pharmaceutical agents. Its derivatives are endowed with many pharmacological properties, such as hypoglycemic, analgesic, anti-inflammatory, antibacterial, anti-HIV, and anticancer[7] activity, as well as useful activities in conditions like schizophrenia, hypertension, and Alzheimer's disease.[8] In addition, they also have agrochemical properties including herbicidal and soil fungicidal activity, thus they have been used as pesticides and insecticides.[9] Among the derivatives of isoxazole, isoxazolopyridine has evoked people's interest and concern because it showed muscle relaxant, anticonvulsant, and CNS depressant activities.[10] To the best of our knowledge, modification and synthesis of polycyclic-fused isoxazolopyridine has never been reported. Thus synthesis of structurally diverse isoxazole-based[11] small molecules is of great significance.

Now, with growing concern over the environmental impact of chemicals, cleaner green reaction conditions in synthetic processes have been advocated. The tight legislation to maintain greenness requires us to prevent the generation of waste, avoid use of auxiliary substances (e.g., organic solvents, additional reagents), and minimize the energy requirement.[12] In addition, reactions in aqueous medium have gained considerable momentum.[13−15]

* To whom correspondence should be addressed. Phone: 0086-516-83500065. Fax: 0086-516-83500065. E-mail: laotu2001@263.net.

As a continuation of our interest in green synthesis and our previous work[16] on the preparation of small heterocyclic with interesting biological properties, herein we report a green, one-pot, efficient synthesis of novel polycyclic-fused isoxazolo[5,4-*b*]pyridines under microwave irradiation in water (Scheme 1).

Results and Discussion

The choice of an appropriate reaction media is of crucial importance for successful microwave promoted synthesis. Initially, the three-component reaction of 4-fluorobenzaldehyde **1a** (1 mmol), 3-methylisoxazol-5-amine **2** (1 mmol), and tetronic acid **3** (1 mmol) was investigated to establish the feasibility of the strategy and optimize the reaction conditions; reaction temperature and different solvents (including ethylene glycol, ethanol, HOAc and water) were screened in the model reaction. All the reactions were proceeded at 90 °C and 200 W. The results were shown in Table 1, water showed a superior advantage not only in promoting the reaction but also in isolation procedure, and

Scheme 1

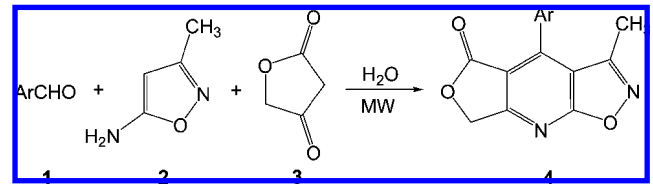

Table 1. Optimization of Reaction Conditions in the Synthesis of Compound **4a**

entry	solvent[a]	*T* (°C)	time (min)	yield[b] (%)
1	ethylene glycol	90	10	43
2	ethanol	90	11	54
3	HOAc	90	10	57
4	H_2O	90	10	65
5	H_2O	100	9	81
6	H_2O	110	7	89
7	H_2O	120	6	91
8	H_2O	130	6	88

[a] The volume of solvent is 2.0 mL. [b] Isolated yields.

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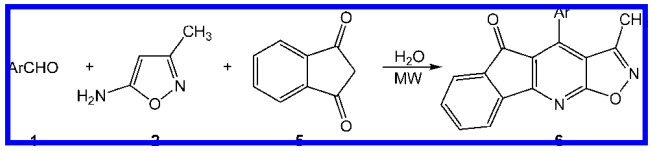
Table 2. Synthesis of Compounds **4** and **6** under Microwave Irradiation Conditions

entry	products	Ar	time (min)	yield[a] (%)	mp (°C)
1	**4a**	4-FC_6H_4	6	91	230–232
2	**4b**	3,4-$OCH_2OC_6H_3$	6	88	272–275
3	**4c**	3,4-$(CH_3O)_2C_6H_3$	6	90	209–212
4	**4d**	3,4,5-$(CH_3O)_3C_6H_2$	6	86	205–208
5	**4e**	3-$NO_2C_6H_4$	5	88	187–188
6	**4f**	4-OH-3-$NO_2C_6H_3$	3	89	249–252
7	**4g**	4-$CH_3OC_6H_4$	5	91	231–233
8	**4h**	3-FC_6H_4	7	84	151–153
9	**6a**	4-FC_6H_4	6	88	254–257
10	**6b**	4-ClC_6H_4	5	90	272–276
11	**6c**	4-BrC_6H_4	5	93	267–270
12	**6d**	4-$CH_3OC_6H_4$	7	91	212–214
13	**6e**	4-$CH_3C_6H_4$	8	90	254–257
14	**6f**	2,4-$Cl_2C_6H_3$	6	89	260–262
15	**6g**	2-ClC_6H_4	7	92	233–235
16	**6h**	3-$NO_2C_6H_4$	6	94	287–290
17	**6i**	3,4-$OCH_2OC_6H_3$	8	92	278–280
18	**6j**	3,4-$(CH_3O)_2C_6H_3$	6	89	228–230

[a] Isolated yields.

Scheme 2



the best yield was achieved (Table 1, entry 4). Thus water was employed as the reaction media for the following reactions.

To further optimize reaction conditions, similar test was carried out at temperatures ranging from 100 to 130 °C, with an increment of 10 °C each time. The yield of product **4a**was increased and the reaction time was shortened as the temperature increased from 100 to 120 °C (Table 1, entries 5−7). However, further increase of the temperature to 130 °C failed to improve the yield (Table 1, entry 8). Therefore, 120 °C was chosen as the most suitable reaction temperature for substituted aromatic aldehydes to take part in reactions.

Under the conditions described above [H_2O, 120 °C, 200W (maximum power)], the scope of these MCRs was examined

Table 3. Synthesis of Compounds **8**, **10**, and **12** under Microwave Irradiation Conditions

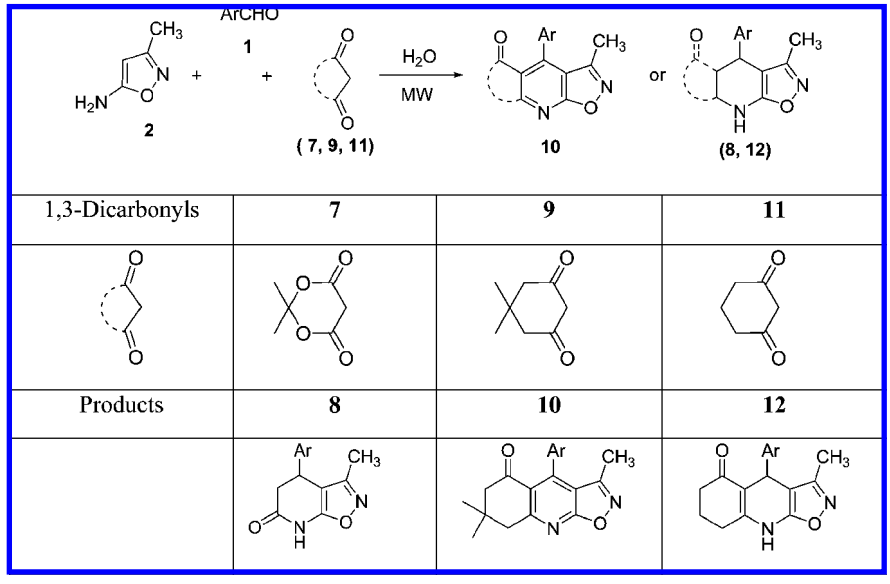
entry	products	Ar	time (min)	yield[a] (%)	mp (°C)
1	**8a**	4-FC_6H_4	7	93	204–207
2	**8b**	4-ClC_6H_4	7	95	235–237
3	**8c**	4-BrC_6H_4	6	95	238–241
4	**8d**	2,4-$Cl_2C_6H_3$	6	92	190–191
5	**8e**	4-$NO_2C_6H_4$	6	90	200–202
6	**8f**	3-$NO_2C_6H_4$	7	90	208–211
7	**8g**	4-OH-3-$NO_2C_6H_3$	6	87	203–206
8	**8h**	4-$CH_3C_6H_4$	9	94	195–196
9	**8i**	4-$OCH_3C_6H_4$	9	94	195–198
10	**8j**	3,4-$OCH_2OC_6H_3$	8	92	189–190
11	**8k**	C_6H_5	9	90	182–184
12	**8l**	2-FC_6H_4	8	93	194–195
13	**10a**	4-FC_6H_4	4	85	216–218
14	**10b**	4-ClC_6H_4	4	87	272–274
15	**10c**	4-BrC_6H_4	4	87	272–275
16	**10d**	4-$NO_2C_6H_4$	3	89	235–238
17	**10e**	2,4-$Cl_2C_6H_3$	4	86	231–233
18	**10f**	4-$CH_3C_6H_4$	6	86	246–248
19	**10g**	4-$CH_3OC_6H_4$	6	88	171–173
20	**10h**	3-$NO_2C_6H_4$	5	83	173–176
21	**12a**	2,4-$Cl_2C_6H_3$	5	84	265–267
22	**12b**	4-$CH_3OC_6H_4$	6	92	218–222
23	**12c**	3,4-$(CH_3O)_2C_6H_3$	6	90	253–256
24	**12d**	3,4,5-$(CH_3O)_3C_6H_2$	6	90	245–248
25	**12e**	4-BrC_6H_4	4	95	228–230
26	**12f**	4-$CH_3C_6H_4$	6	93	226–229

[a] Isolated yields.

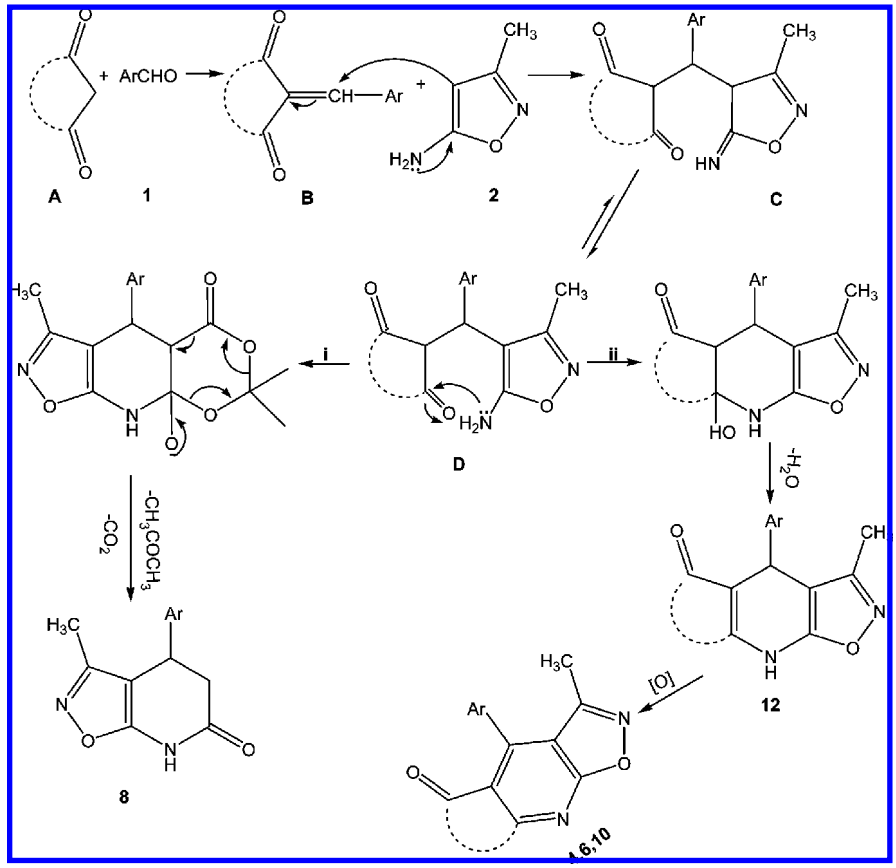
(Table 2). A range of novel valuable structures of **4** were synthesized in good to excellent yields by simply microwave heating. The results are summarized in Table 2. Aromatic aldehydes bearing both electron-withdrawing group (EWG) and electron-donating group (EDG) proceeded smoothly in this reaction and afforded the desired derivatives. However, when the aliphatic aldehyde was applied to this reaction, no expected product was obtained.

Subsequently, another active methylene compound, 1,3-indanedione was examined as the replacement of tetronic acid in the reaction with aromatic aldehydes and 3-methyl-isoxazol-5-amine (Scheme 2). To our delight, under the optimized conditions described above, another series of isoxazolo[5,4-*b*]pyridines **6** were easily generated (Table 2).

Scheme 3



Scheme 4. Possible Mechanism for the Formation of Products **4**, **6**, **8**, **10**, and **12**



To be a safe, readily available and environmentally friendly solvent, water appears to be a popular reaction medium because of its nontoxic, noncorrosive and nonflammable nature.[17] Under microwave (MW) irradiation, water is rapidly heated to high temperatures, and act as a less polar pseudo-organic solvent.[18] So microwave-assisted organic reaction in water has become an important research area.[19]

With the desired products can be easily obtained, we set out for the study of more challenging examples. As a check of the versatility of our method, its application to the preparation of other polycyclic-fused isoxazolo[5,4-*b*]pyridines was studied (Scheme 3). The results are summarized in Table 3.

Under the above-mentioned same reaction conditions, all the reactions proceeded smoothly. It is worthy of noting that this chemistry offered the 1,4-dihydropyridines (1,4-DHPs) **12**, which went no further to dehydrogenation, when cyclohexane-1,3-dione take part in the reaction. This is still a puzzle to us, and further efforts are underway to clarify this reason.

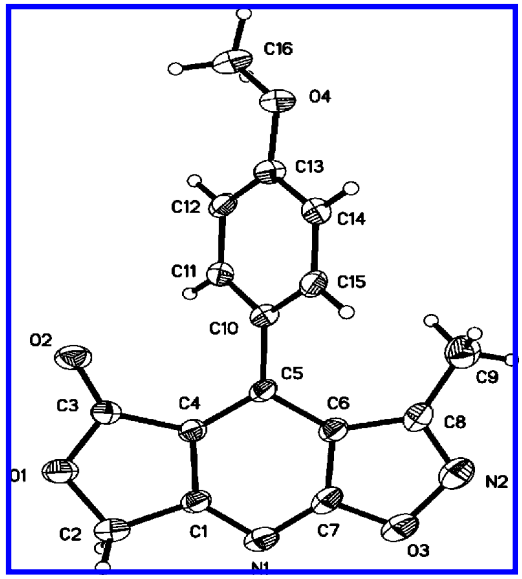


Figure 1. ORTEP drawing of **4g**.[20]

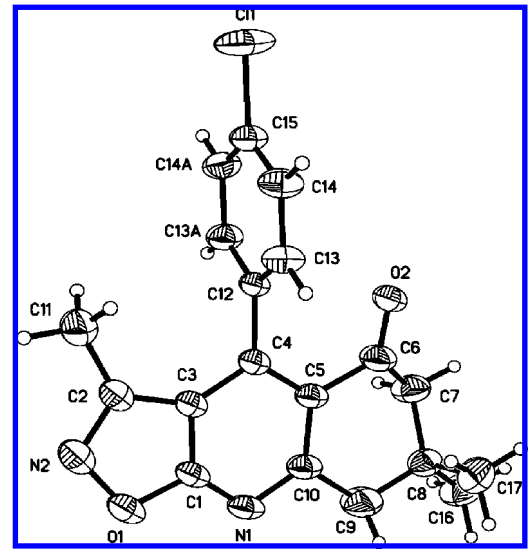
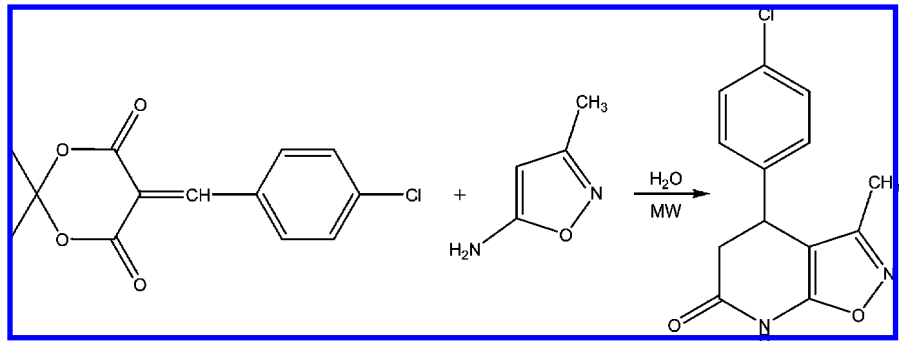


Figure 2. ORTEP drawing of **10b**.[20]

Scheme 5



The products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS. Furthermore, the structures of **4g** and **10b** were established by X-ray crystallographic analysis (Figure 1 and Figure 2).[20]

Proposed Reaction Mechanism. Although the mechanism of the reaction has not yet been established, a possible explanation is proposed in Scheme 4.

The reaction might proceed via sequential condensation, addition, cyclization, and elimination. First, a condensation between 1,3-dicarbonyl compounds **A** with aldehydes **1** to afford intermediate **B**. The Michael addition of **B** with 3-methylisoxazol-5-amine **2** would then furnish the intermediate product **C**, which isomerized to **D**. When the 1,3-dicarbonyl compound is Meldrum's acid, the intermediate product **D** subsequently underwent intramolecular cyclization and then released acetone and carbon dioxide to give compounds **8**. Another case is that, when the rest 1,3-dicarbonyl compounds take part in the reactions, the intermediate product **D** then underwent dehydration and dehydrogenation to generate the target products **4**, **6**, **10**, and **12**.

Evidence supporting this proposed mechanism was provided by the following reaction (Scheme 5).

To our delight, under the same reaction condition, the expected product was obtained in a yield similar to that obtained in the one-pot reaction.

Conclusion

In brief, a convenient, clean, and efficient method was developed for the generation of polycyclic-fused isoxazolo[5,4-*b*]pyridine, which may present potential biological activities. These compounds were prepared in water, an excellent solvent in terms of environmental impact and with reduced waste production. In addition, the procedure offers several advantages, including operational simplicity, and increases safety for small-scale high-speed synthesis, which makes it a useful and attractive process for library generation in drug discovery efforts.

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Supporting Information Available. Representative experimental procedures, spectral data of compounds **4a**−**h**, **6a**−**j**, **8a**−**l**, **10a**−**h**, and **12a**−**f**, and crystallographic information files (CIF) of **4g** and **10b**. This information is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Maclean, D.; Baldwin, J. J.; Ivanov, V. T.; Kato, Y.; Shaw, A.; Schneider, P.; Gordon, A. E. M. *J. Comb. Chem.* **2000**, *2*, 562.
(2) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1996**, *52*, 4527.
(3) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643.
(4) Dolle, R. E.; Nelson, K. H. *J. Comb. Chem.* **1999**, *1*, 235.
(5) Dolle, R. E. *J. Comb. Chem.* **2000**, *2*, 383.
(6) (a) Tan, D. S. *Nat. Chem. Biol.* **2005**, *1*, 74. (b) Hoesl, C. E.; Nefzi, A.; Houghten, R. A. *J. Comb. Chem.* **2003**, *5*, 155.
(7) (a) Shin, K. D.; Lee, M. Y.; Shin, D. S.; Lee, S.; Son, K. H.; Koh, S.; Paik, Y. K.; Kwon, B. M.; Han, D. C. *J. Biol. Chem.* **2005**, *280*, 41439. (b) Demers, J.; Hageman, W.; Johnson, S.; Klaubert, D.; Look, R.; Moore, J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2451. (c) Simoni, D.; Roberti, M.; Paolo, I. F.; Rondanin, R.; Baruchello, R.; Malagutti, C.; Mazzali, A.; Rossi, M.; Grimaudo, S.; Capone, F.; Dusonchet, L.; Meli, M.; Raimondi, M. V.; Landino, M.; D'Alessandro, N.; Tolomeo, M.; Arindam, D.; Lu, S.; Benbrook, D. M. *J. Med. Chem.* **2001**, *44*, 2308.
(8) (a) Rowley, M.; Broughton, H. B.; Collins, I.; Baker, R.; Emms, F.; Marwood, R.; Patel, S.; Patel, S.; Ragan, C. I.; Freedman, S. B.; Leeson, P. D. *J. Med. Chem.* **1996**, *39*, 1943. (b) Wittenberger, S. J. *J. Org. Chem.* **1996**, *61*, 356. (c) Dannhardt, G.; Dominiak, P.; Laufer, S. *Arznei-Forschung.* **1993**, *43*, 441.
(9) Pinho, e M.; Teresa, M. V. D. *Curr. Org. Chem.* **2005**, *9*, 925.
(10) Tatee, T.; Narita, K.; Kurashige, S.; Ito, S; Miyazaki, H.; Yamanaka, H.; Mizugaki, M.; Sakamoto, T.; Fukuda, H. *Chem. Pharm. Bull.* **1987**, *35*, 3676.
(11) (a) Pevarello, P.; Amici, R.; Brasca, M. G.; Villa, M.; Varasi, M. *Targets Heterocycl. Syst.* **1999**, *3*, 301. (b) Chande, M. S.; Verma, R. S.; Barve, P. A.; Khanwelkar, R. R.; Vaidya, R. B.; Ajaikumar, K. B. *Eur. J. Med. Chem.* **2005**, *40*, 1143.
(12) Tundo, P.; Anastas, P.; Black, D. S.; Breen, J.; Collins, T.; Memoli, S.; Miyamoto, J.; Polyakoff, M.; Tumas, W. *Pure Appl. Chem.* **2000**, *72*, 1207.
(13) Chankeshwara, S. V.; Chakraborti, A. K. *Org. Lett.* **2006**, *8*, 3259.
(14) Khatik, G. L.; Kumar, R.; Chakraborti, A. K. *Org. Lett.* **2006**, *8*, 2433.
(15) Hailes, H. C. *Org. Process Res. Dev.* **2007**, *11*, 114.
(16) (a) Tu, S. J.; Zhang, Y.; Zhang, J. Y.; Jiang, B.; Jia, R. H.; Zhang, J. P.; Ji, S. J. *Synlett* **2006**, 2785. (b) Tu, S. J.; Jia, R. H.; Jiang, B.; Zhang, J. Y.; Zhang, Y.; Yao, C. S.; Ji, S. J. *Tetrahedron* **2007**, *63*, 381. (c) Tu, S. J.; Zhang, Y.; Jiang,

H.; Jiang, B.; Zhang, J. Y.; Jia, R. H.; Si, F. *Eur. J. Org. Chem.* **2007**, *9*, 1522.
(17) Polshettiwar, V.; Varma, R. S. *Chem. Soc. Rev.* **2008**, *37*, 1546.
(18) (a) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (b) Gellis, A.; Boufatah, N.; Vanelle, P. *Green Chem.* **2006**, *8*, 483.
(19) (a) Wu, X.; Larhed, M. *Org. Lett.* **2005**, *7*, 3327. (b) Wu, X.; Ekegren, J. K.; Larhed, M. *Organometallics* **2006**, *25*, 1434. (c) Ju, Y.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 135. (d) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563.
(20) The single-crystal growth was carried out in ethanol at room temperature. X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer (graphite monochromator, MoKa radiation λ = 0.71073 Å). Crystal data for **4g**: Empirical formula $C_{16}H_{12}N_2O_4$, Formula weight 296.28, crystal dimension 0.14 × 0.11 × 0.05 mm, monoclinic, space group *P2(1)/c*, a = 13.8513(16) Å, b = 7.6116(11) Å, c = 12.6732(15) Å, α = 90, β = 95.5920(10), γ = 90, μ = 0.108 mm^{-1}, V = 1329.8(3) $Å^3$, Z = 4, Dc = 1.480 Mg/m3, $F(000)$ = 616, S = 1.025, R_1 = 0.0575, wR_2 = 0.0806. Crystal data for **10b**: Empirical formula $C_{19}H_{17}ClN_2O_2$, Formula weight 340.80, crystal dimension 0.17 × 0.18 × 0.05 mm, Orthorhombic, space group *Pnma*, a = 11.7147(14) Å, b = 6.9466(9) Å, c = 20.785(2) Å, α = 90, β = 90, γ = 90, μ = 0.239 mm^{-1}, V = 1691.4(3) $Å^3$, Z = 4, Dc = 1.338 Mg/m3, $F(000)$ = 712, S = 1.032, R_1 = 0.0560, wR_2 = 0.1294.

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